REMARKS

I. Status of the Claims

Applicant elected Group I and acetaminophen as species, the latter with traverse.

Claims 1-15, are pending.

Claims 1, 13, and 24 are amended, Claim 30 is amended, although not in the elected group, to preserve right of rejoinder.

Claim 4 and 10 are cancelled.

Claims 16-37 are withdrawn.

II. Summers does not teach all claim elements

Claims 1-12 were rejected under 35 USC §102 (e) by Summers.

Claim 1 is amended to be limited to only other ingredients disclosed.

The '797 patent claims "a health supplement composition" (that is, a nutional supplement) "for improving memory and cognitive abilities." The composition **requires**:

a. at least one phosphoester in a daily amount of 5-10,000 mg, and

b. at least one antioxidant.

U.S. Application 10/813,760, Joel Bernstein inventor ('760) has **no** phosphoester whatsoever in its claims. The '760 application **requires** a hepatotoxic compound in its compositions whereas **no** hepatotoxic compound is taught or claimed as part of the compositions described in the '797 patent. Finally, the most potent antioxidant vitamins, Vitamin A, Vitamin C, and Vitamin E are not included in any of the compositions taught or claimed in the '760 application. This is because antioxidant activity is completely unrelated to the ability of a compound to mitigate liver toxicity of a hepatotoxic compound. Summers does not anticipate all elements of claim 1, and claim 2-12 are dependent so have the same limitations.

III. A *prima facie* case of obviousness is not established

Claim 1-15 were rejected under 350 USC §103 (e) over/ Kroger and Yang.

A *prima facie* case of obviousness is not established.

The '757 patent (Yang) claims a method and compositions of treating acetaminophen overdose by administering an agent comprising daillyl sulfone within about 6-24 hours after an overdose of acetaminophen has been ingested. It further provides that N-acetyl cysteine, L-

methionine, L-cysteine (compounds with sulfhydryl groups) and mixtures thereof can be added to the daillyl sulfone if desired.

In contrast, the '760 application teaches compositions that contain acetaminophen and mixtures of nicotinamide and methionine, or acetaminophen and mixtures of nicotinamide, methionine and folic acid. The '757 patent neither teaches nor claims any combination or formulation of these agents and acetaminophen. The composition and method claims of the '757 patent require daillyl sulfone. In contrast, the '760 application neither teaches nor claims daillyl sulfone. Furthermore, the '757 patent's teachings are for compositions containing solely agents which "supply sulfhydryl groups." Neither nicotinamide nor folic acid contains a sulfhydryl group in the molecules.

There are three critical aspects of the pending claims which are not taught by the Kroger Papers:

a. Route of administration – In the Kroger Papers, nictinamide or methionine or their combination are administered intaperitoneally ("IP"). This is a very substantive difference from the routes of administration claimed in the '760 application. First, IP is virtually never used in humans [1,2] for two principal resons: (a) IP provides significantly faster and more substantial blood levels of drugs [1,3] than other routes of administration. (b) risk of infection and local adhesions are unwarranted for use of this route in humans [1] . There are no drugs approved for IP administration to humans in North America or Europe.

b. Composition and Method – In the Kroger Papers, nictinamide and/or methinonine are administered as separate IP injections and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, the compositions cited in the '760 application, all components (the hepatotoxic active drug agent and the hepatoprotective agents, nictinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).

c. The dosages of nicotinamide and methionine administered IP for protective effects in the Kroger papers are very substantially greater then those in the '760

> application. IP dosages in the Kroger Papers range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans [4] the dosage of nicotinamide in the claims of the '760 application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims of the '760 application ranges from .29 mg/kg to 5.7 mg/kg for males and from .33 mg/kg to 6.7 mg/kg for females. IP injection results in much higher and much faster peak blood levels of drug. In the '760 application, these dosages are provided orally or by injection **not into** the peritoneum. Consequently, the dosages of nicotinamide and methionine in present claims are minuscule compared to the Kroger papers.

The discussion of these differences renders it clear that the Kroger papers do not teach that much lower dosages of nicotinamide and methionine, administered in a single dosage from with a hepatotoxic drug (e.g. capsule, tablet, solution), given by completely different routes of administration than Kroger, would provide safe and effective hepatoprotection from a hepatotoxic drug.

To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc. et al.* 776 F. 2d 281, (CAFC 1985), Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *In re Vaeck* 947 F. 2d 488, (CAFC 1991). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious, *Ex parte Hiyamizu* 10 PQ. 2d 1393 (BPAI 1988), absent evidence of a motivating force which would impel persons skilled in the art to do what applicant has done. *Ex parte Levengood* 28 PQ. 2d 1300 (BPAI 1993). The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* 229 F. 2d 476 (CCPA 1956). Obviousness

requires a suggestion of all limitations in a claim ". *CFMT, Inc. v. Yieldup Int'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003). One cannot simply backtrack from the invention to find a connection to the prior art. Hindsight must be avoided. *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

IV. **Claims 1-12 are enabled for "a hepatotoxic compound"**

Applicant elected acetaminophen as a species for purposes of searching as required by the examiner. The other hepatotoxic compounds in claim 13 all have in common that they produce hepatotoxicity in the same fashion. This would be recognized by those of skill in the art. A declaration can be provided to show results in methatrexate and divalproex, if that would allow claims to "hepatotoxic compounds."

V. **Other**

Exhibit A provides information on dosages and administration known in the art.

No fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41959-102739).

Respectfully submitted,

Alice O. Martin
Registration No. 35,601
Attorney for Applicant

Dated: DRAFT

Barnes & Thornburg LLP
P.O. Box 2786
Chicago, IL 60690-2786